Review Article

Current Concepts

SCREENING FOR LUNG CANCER

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LUNG cancer is the leading cause of death from cancer among men and women in the United States. More people die each year of lung cancer than of colon, breast, and prostate cancer combined. Despite new diagnostic techniques, the overall five-year survival rates remain about 14 percent, and most patients still present with advanced disease.[1]

There has long been interest in screening to detect lung cancers when they are smaller and presumably at earlier and more curable stages, as witnessed by the support for previous screening trials using chest radiography and cytologic examination of sputum. Unfortunately, these studies failed to reach the ultimate goal of a diagnostic screening test — a decrease in disease-specific mortality. The screened groups had the same number of deaths from lung cancer as the control groups, and screening was effectively abandoned.

With the development of newer forms of technology, there has been a resurgent interest in screening for lung cancer, and patients have requested the examination after learning of the new possibilities through the media. Data obtained from subjects at the time of study entry (prevalence-screening data) from recent trials using low-dose computed tomography (CT) suggest that this technique could save lives in persons at high risk. These data, however, are often confusing. Before any new screening recommendations are made, detailed analyses of the CT trials are needed, including analyses of morbidity and mortality data as well as a cost–benefit study. We review screening for lung cancer, including prior trials, ongoing early-detection studies, potential limitations, and recommendations based on published data.

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SOME FUNDAMENTALS ABOUT SCREENING

Screening is performed to detect disease at a stage when cure or control is possible.[2,3] It presumes that a test or series of tests will identify asymptomatic persons at risk for a specific disease. Persons with a positive result on screening can be further evaluated to determine whether they actually have the disease. Ideally, once the diagnosis is established, early intervention should change the course of the disease, resulting in decreased mortality (the number of disease-specific deaths relative to the total number of persons evaluated). Although survival from the time of diagnosis of the disease is commonly reported in screening trials, it is not an appropriate measure of a diagnostic screening test and can be misleading because it is subject to lead-time bias (Fig. 1), length-time bias (Fig. 2), and overdiagnosis bias (Fig. 3).[2,3] An effect on mortality rather than survival is necessary to validate potential screening methods.

The principles of screening can be applied to lung cancer, but success depends on several basic assumptions. There must be effective treatment at the preclinical (asymptomatic) stage that can reduce mortality in the screened group as compared with the unscreened group. In addition, the sensitivity, specificity, accessibility, cost, and associated morbidity of the screening tests must be reasonable.

PRIOR SCREENING TRIALS

In the 1950s, four nonrandomized, uncontrolled screening studies were performed. Two trials conducted in the United States, the Philadelphia Pulmonary Neoplasm Research Project[4] and the Veterans Administration trial,[5] enrolled approximately 20,000 patients, and neither showed a benefit from screening chest radiography. Two additional screening studies, the Tokyo Metropolitan Government Study[6] and the South London Lung Cancer Study,[7] conducted chest radiography surveys. These studies suggested that there was some improvement in survival, but mortality from lung cancer could not be adequately assessed.

1966
1966
1982
1968

Following these studies were two nonrandomized, controlled trials, the North London Cancer Study in 1959 and the Erfurt County study in 1972.[8,9] All patients underwent chest radiography on entry, and in both studies the screened group underwent radiography every six months thereafter. Whereas the control group in the London study underwent follow-up chest radiography at the end of the trial (at four years), the control group in the Erfurt study underwent chest radiography every one to two years. In

1968
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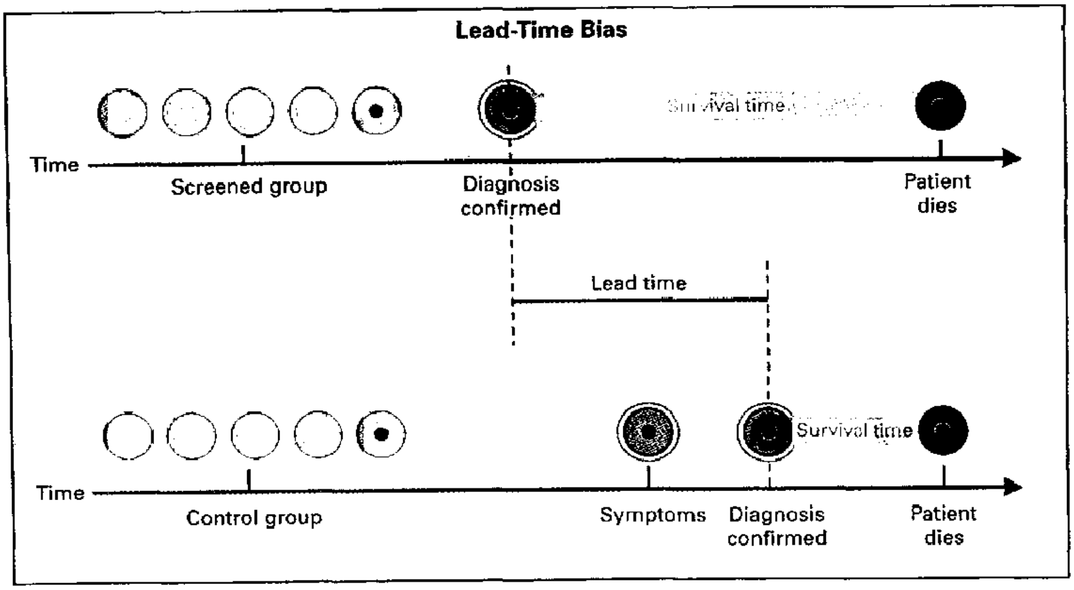

Figure 1. Lead-Time Bias.

In the example shown, the diagnosis of disease is made earlier in the screened group, resulting in an apparent increase in survival time (lead-time bias), although the time of death is the same in both groups.

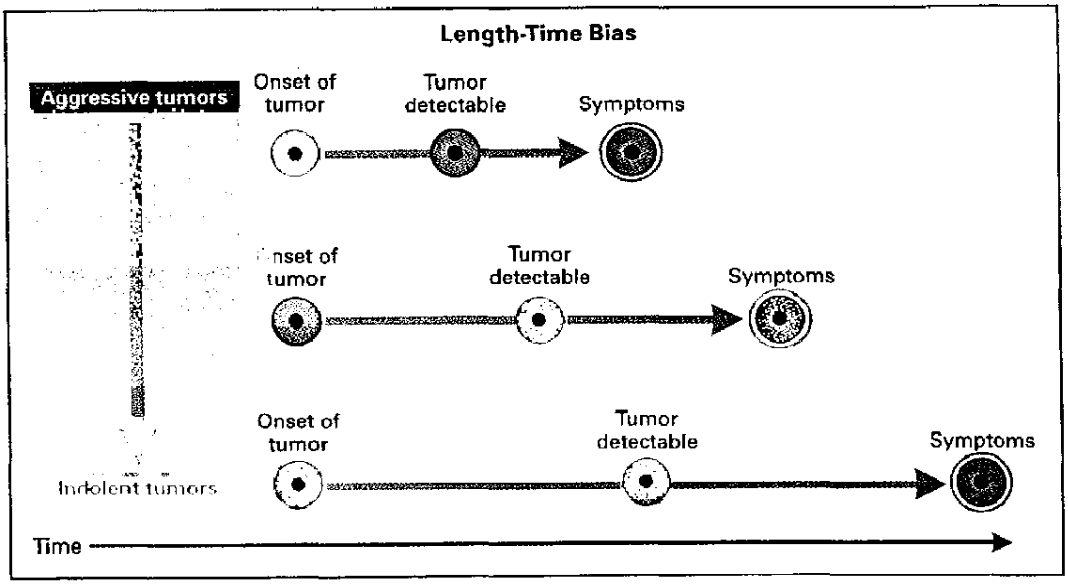

Figure 2. Length-Time Bias.

The probability of detecting disease is related to the growth rate of the tumor. Aggressive, rapidly growing tumors have a short potential screening period (the interval between possible detection and the occurrence of symptoms). Thus, unless the screening test is repeated frequently, patients with aggressive tumors are more likely to present with symptoms. More slowly growing tumors have a longer potential screening period and are more likely to be detected when they are asymptomatic. As a result, a higher proportion of indolent tumors is found in the screened group, causing an apparent improvement in survival.

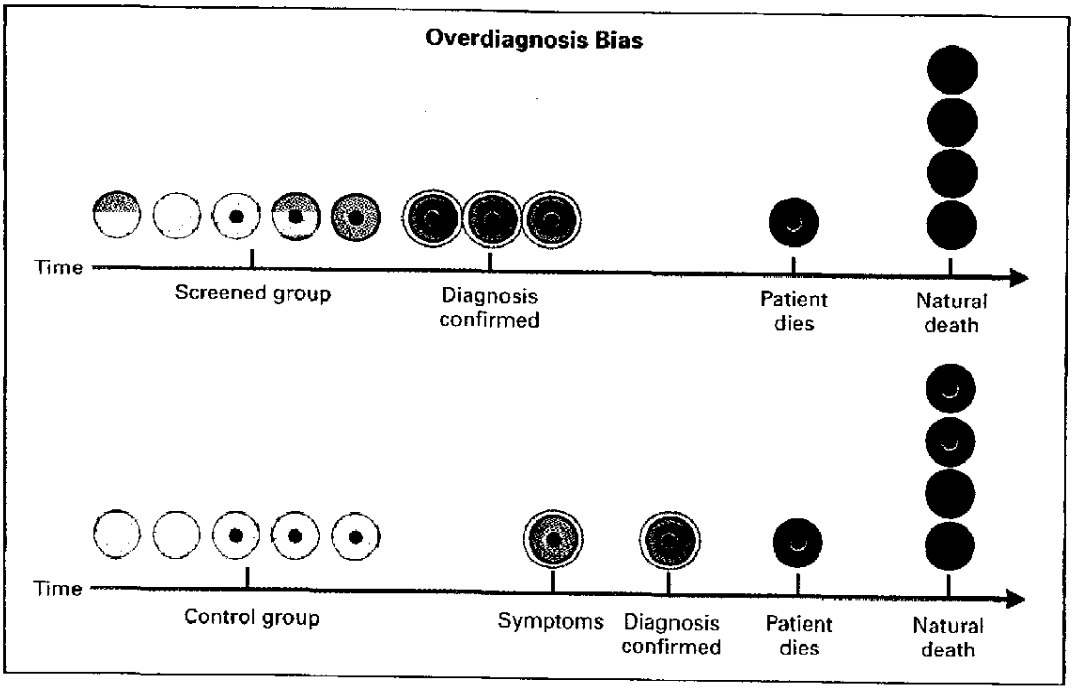

Figure 3. Overdiagnosis Bias.

Overdiagnosis bias is an extreme form of length-time bias. The detection of very indolent tumors in the screened group produces apparent increases in the number of cases of lung cancer (three in the screened group in the figure and one in the control group) and in survival (two of three patients in the screened group were treated and died of natural causes, without evidence of disease [66 percent survival], and the one patient in the control group did not survive [0 percent survival]), with no effect on mortality (one death from lung cancer in each group). Two patients in the control group died with undiagnosed lung cancer that did not affect their natural life span.

both trials, the number of early-stage lung cancers, the number of patients whose cancers could be resected, and the survival rates were higher in the screened groups. There was, however, no clear reduction in mortality from lung cancer in the screened groups as compared with the control groups.

In the early 1970s, four randomized, controlled trials using chest radiography and cytologic examination of sputum targeted high-risk male smokers over 45 years of age. In the Johns Hopkins Lung Project[10] and the Memorial Sloan-Kettering Lung Project,[11] participants were randomly assigned to a group undergoing dual screening (annual chest radiography and a sputum cytologic examination every four months) or to a control group undergoing annual chest radiography. In the Mayo Lung Project,[12] participants were offered chest radiographic and sputum cytologic examinations at enrollment. They were then randomly assigned to a close-surveillance group, which underwent chest radiographic and sputum cytologic examination at four-month intervals, or to a control group, which was advised to have the standard surveillance of yearly chest radiography and sputum analysis. A similar design was used in a Czechoslovakian study,[13] although the control group underwent its first reexamination by chest radiography and sputum analysis three years after entering the trial and underwent repeated chest radiography only at years 4, 5, and 6. These randomized trials enrolled approximately 37,000 people.

Extensive analysis of these four trials has revealed a number of expected and unexpected findings.[14-17] These studies, like prior nonrandomized trials, reported an increased incidence of earlier-stage lung cancers, more resectable cancers, and improved five-year survival rates in the screened groups as compared with the control groups (35 percent vs. 15 percent). In the final analysis, however, as in previous studies, there was no statistically significant difference in mortality attributable to lung cancer between the two groups.[18] Patients with lung cancer in the screened groups had a higher likelihood of undergoing surgical resection and lived longer than those in the control groups, but equal numbers of patients in both groups ulti-

mately died from their disease. Several hypotheses have been advanced to explain the findings (including lead-time and overdiagnosis bias); the conclusion was that screening and subsequent therapy did not affect the outcome of the disease.

In addition, several findings are sobering. First, in the Johns Hopkins Lung Project, approximately 50 percent of the patients in whom lung cancer developed had negative findings at the time of screening and manifested symptoms before the next scheduled follow-up. This suggests that some lung cancers are very aggressive and that even close surveillance and early detection will not affect the outcome. Second, some of the patients with small primary lesions already had metastases. Thus, the size of the primary lesion was not always correlated with the ability of the tumor to disseminate. Finally, it was predicted that the screened group would have more patients with early-stage disease (stages I and II) and fewer with advanced disease (stages III and IV) than the control group ("stage shift"), but that the total number of cases of lung cancer in each group would be the same. Although more cases of early-stage disease were indeed found in the screened group than in the control group (240 vs. 212), the number of patients with advanced-stage disease was not lower in the screened group than in the control group (303 vs. 304).[17] The predicted stage shift did not occur. In all three U.S. studies, there were more cases of lung cancer in the screened group than in the control group. Perhaps some of these additional cancers found by screening were not clinically relevant and, if undetected, would never have affected the patients. In other words, the screening may have led to the overdiagnosis of lung cancer.

CURRENT EARLY-DETECTION AND SCREENING TRIALS

Imaging Studies

The results of previous trials have been questioned and criticized. Concern about study design, statistical analysis, contamination, inherent biases, and older forms of technology has prompted new early-detection trials using improved diagnostic-imaging techniques[19-21] (Table 1). The prevalence-screening data from three trials have been published. The two nonrandomized studies from Japan used chest radiography, low-dose CT, and examination of a three-day pooled sputum sample for screening.[22,23] A third trial, the Early Lung Cancer Action Project, has enrolled 1000 high-risk smokers over the age of 60 years. This trial has a nonrandomized design and uses chest radiography and low-dose CT.[24]

The results of these trials have confirmed that CT is more sensitive than conventional chest radiography for the detection of lung nodules and that some of these nodules prove to be lung cancer. If the data from the low-dose CT studies are analyzed in the same way and directly compared with the data from previous trials using chest radiography and sputum cytologic examination, it is found that CT detects more cases of lung cancer (27 per 1000 vs. 9.1 to 7.6 per 1000) and that more patients screened by CT have resectable early-stage disease. Unfortunately, as with the previous screening attempts, the prevalence-screening rates for advanced disease on low-dose CT did not decrease when compared with rates in the dual-screening groups (3.0 per 1000 participants vs. 3.8 to 2.1 per 1000). Thus, it remains to be seen whether a stage shift will result when low-dose CT is used for screening. One might again surmise that without a stage shift there will be no decrease in mortality with use of low-dose CT screening.

The true clinical significance of the small tumors found by screening is unknown, and their effect on mortality awaits future investigation. Given the design and objectives of these nonrandomized trials, however, only inferences regarding mortality from lung cancer will be possible.

In addition to detecting an increased number of lung cancers, low-dose CT found at least one indeterminate nodule in 23 percent of all screened patients.[24] The majority should be benign, but evaluation of all these nodules is not a trivial problem. This could create a very expensive clinical quagmire. The effects of evaluating these nodules on morbidity and mortality remain to be determined.

Several additional studies are currently under way, but only preliminary prevalence-screening data are available. In 1999 the Mayo Clinic enrolled 1520 current or former smokers in a nonrandomized trial. All the patients underwent base-line low-dose CT and sputum cytologic examination, and they will have an annual follow-up for three consecutive years. The preliminary results of this study show 15 patients with lung cancer, 60 percent of whom had early-stage disease. Unfortunately, 51 percent of all the patients had at least one nodule and required frequent (every three months), serial follow-up CT examinations. A trial at the University of Münster enrolled 919 participants. Lung cancer has been diagnosed in 13 patients (prevalence, 1.4 percent), 8 of whom (62 percent) had stage I disease.

After extensive discussions of study design, several groups are now proposing prospective, randomized, controlled trials using low-dose CT. One cooperative group sponsored by the National Cancer Institute, the American College of Radiology Imaging Network, has designed a multicenter, randomized, controlled trial of 7000 persons at high risk.[25] The participants will be assigned to either yearly low-dose CT (screening group) or no chest radiography (control group) in equal numbers. The study was designed to detect a 50 percent reduction in cumulative mortality from lung cancer. The National Cancer Institute is also considering an even larger trial, with

TABLE 1. SUMMARY OF CURRENT LOW-DOSE CT SCREENING PROGRAMS FOR LUNG CANCER.*

STUDY FEATURES	NATIONAL CANCER CENTER HOSPITAL, JAPAN	SHINSHU UNIVERSITY, JAPAN	EARLY LUNG CANCER ACTION PROJECT, UNITED STATES	MAYO CLINIC, UNITED STATES	UNIVERSITY OF MONSTER, GERMANY
Eligibility criteria					
Smoking history	>20 pack-yr suggested	No requirement	≥10 pack-yr	Current or former smoker (quit <10 yr before study), ≥20 pack-yr	≥20 pack-yr suggested
Age — yr	≥50 suggested	>40	>60	≥50	≥40 suggested
Prior cancer	Not reported	Not reported	No	None within previous 5 yr	No
Frequency of screening					
CT	Biannual	Annual	Annual	Annual	Annual
Chest radiography	Biannual	Annual	Annual	None	Not reported
Study results					
No. of participants	1369 (3457 examinations)†	5483	1000	1520	919
Nodules — no. (%)	Not reported	Not reported	233 (23)	782 (51)	Not reported
Lung cancer — no. (%)	15 (0.43)‡	19 (0.35)	27 (2.7)	15 (1)§	13 (1.4)
Stage I disease — no. (%)	14 (93)	16 (84)	23 (85)	9 (60)	8 (62)

*Data are from Kaneko et al.,[22] Sone et al.,[23] and Henschke et al.[24]

†The data reflect both the initial prevalence screening and the results of repeated screening.

‡The value in parentheses is the percentage of all examinations.

§The number of tumors reported through May 2000 is given.

88,000 participants, which should have the power to detect a 20 percent reduction in mortality.

Nonimaging Methods of Early Detection

Whereas current screening trials rely primarily on imaging studies, other methods of early diagnosis are being pursued, although none have been tested in a large trial as the sole detection technique.[26-31] Sputum samples, bronchoalveolar-lavage fluid, and bronchial-biopsy specimens, including those obtained from fluorescence bronchoscopy, have been analyzed for findings associated with neoplasia, such as abnormal patterns of immunostaining, malignant changes, genetic mutations (e.g., in p53 and K-*ras*), telomerase activity, microsatellite instability, and abnormal DNA methylation.[27,28,32-35] Although dysplastic and malignant lesions have been found, the sensitivity and specificity of the tests, particularly for small peripheral lesions, remain suboptimal. These techniques may be able to complement noninvasive imaging studies, although the invasive procedures required to obtain some of these specimens and current limits on their accuracy make their clinical usefulness uncertain.

POTENTIAL BIOLOGIC LIMITATIONS IN SCREENING FOR LUNG CANCER

The ability of CT to identify smaller nodules than those routinely seen on chest radiographs has generated interest in this technique as a potential screening tool. However, the size of the nodule at diagnosis does not necessarily correlate with the clinical outcome. It cannot be assumed that the biologic behavior of lung cancer, the result of a variety of genetic changes, parallels anatomical size. In fact, there are currently no data to confirm that a primary 5-mm lung tumor (about 10^8 cells) has a significantly better prognosis than a 10-mm tumor (about 10^9 cells) or even a 30-mm tumor (about 2.7×10^{10} cells). All these lesions occur late in the course of the disease, since at the time of death patients typically have a tumor burden of about 10^{12} cells. In a recent study of 510 patients with T1N0M0 disease (tumors less than 3 cm in diameter), there was no statistical correlation between small size at diagnosis and survival. Patients with 3-cm masses had the same outcomes as those with nodules less than 1 cm in diameter.[36]

The assumptions that size correlates with biologic behavior and that small lesions are equivalent to early-stage disease have not been confirmed for lung cancer. Tumors may already have demonstrated their potential to remain localized or to metastasize by the time they are visible on CT imaging. In some studies, about 60 percent of patients with clinical (radiographically detected) stage I disease (tumors less than 3 cm in diameter) died from lung cancer within five years despite appropriate therapy.[37] This suggests that a high percentage of patients have disseminated, occult disease at the time of presentation. With newer and more sensitive methods of detection, sites of isolated tumor cells and micrometastases may now become apparent.[38] In fact, clinical studies have confirmed that patients with small tumors can harbor malignant cells in normal-appearing lymph nodes that are detectable only by immunohistochem-

ical or reverse-transcriptase–polymerase-chain-reaction assays.[39-42] Other investigations have found tumor cells in the peripheral blood and bone marrow of patients with lung cancers of all sizes and stages.[43-45]

Finally, a recent experimental study showed that a 1-cm tumor can shed approximately 3 million to 6 million cells into the blood every 24 hours. These cells were less clonogenic and less tumorigenic than those of the primary tumor, but more apoptotic.[46] Other studies have suggested that metastases may occur at the time of angiogenesis, when lesions are approximately 1 to 2 mm in diameter, and perhaps even earlier as tumors coopt adjacent normal blood vessels.[47-50]

CURRENT RECOMMENDATIONS

Although there is public and political pressure, based only on low-dose CT prevalence-screening data, to change clinical practice rapidly and to offer mass lung-cancer screening, there should be no compromise or shortcuts in the rigorous scientific process required to determine whether this practice is justified. Too often, presumed solutions have prematurely become standard medical care before the appropriate studies have been completed.[51,52] We strongly recommend that well-designed studies be conducted, completed, analyzed, and validated before a mass screening program is implemented. Until these trials clearly confirm a reduction in mortality from lung cancer, only carefully monitored studies should enroll patients for lung-cancer screening.

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